Regulation of the CUL3 Ubiquitin Ligase by a Calcium-Dependent Co-adaptor.

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Public Summary:
Aberrant collagen secretion is a major cause for craniofacial abnormalities, as observed in the majority of birth defects. In this work, we discovered a novel, calcium-dependent pathway that is critical for regulating collagen secretion and craniofacial development.

Scientific Abstract:
The ubiquitin ligase CUL3 is an essential regulator of neural crest specification whose aberrant activation has been linked to autism, schizophrenia, and hypertension. CUL3 exerts its roles by pairing with approximately 90 distinct substrate adaptors, yet how the different CUL3-complexes are activated is poorly understood. Here, we show that CUL3 and its adaptor KLHL12 require two calcium-binding proteins, PEF1 and ALG2, for recognition of their substrate SEC31. PEF1 and ALG2 form a target-specific co-adaptor that translates a transient rise in cytosolic calcium levels into more persistent SEC31 ubiquitylation, which in turn triggers formation of large COPII coats and promotes collagen secretion. As calcium also instructs chondrocyte differentiation and collagen synthesis, calcium-dependent control of CUL3KLHL12 integrates collagen secretion into broader programs of craniofacial bone formation. Our work, therefore, identifies both calcium and CUL3 co-adaptors as important regulators of ubiquitylation events that control human development.